IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

SMITHKLINE BEECHAM CORPORATION and BEECHAM GROUP, P.L.C. v. GENEVA PHARMACEUTICALS, INC.	CIVIL ACTION NO. 99-CV-2926 NO. 00-CV-5953
SMITHKLINE BEECHAM CORPORATION, SMITHKLINE BEECHAM P.L.C. and BEECHAM GROUP, P.L.C. v. **APOTEX CORPORATION, APOTEX, INC. and TORPHARM, INC.**	CIVIL ACTION NO. 99-CV-4304 NO. 00-CV-4888 **NO. 01-CV-159** NO. 01-CV-2169 **Judge Richard Barclay Surrick**
SMITHKLINE BEECHAM CORPORATION, SMITHKLINE BEECHAM, P.L.C. and BEECHAM GROUP, P.L.C. v. ZENITH GOLDLINE PHARMACEUTICALS, INC.	CIVIL ACTION NO. 00-CV-1393 NO. 00-CV-6464 NO. 01-CV-2602
SMITHKLINE BEECHAM CORPORATION and BEECHAM GROUP, P.L.C. v. ALPHAPHARM PTY, LTD.	CIVIL ACTION NO. 01-CV-1027 NO. 01-CV-3364
SMITHKLINE BEECHAM CORPORATION and BEECHAM GROUP, P.L.C. v. ANDRX PHARMACEUTICALS, INC., ANDRX PHARMACEUTICALS, L.L.C. and BASF CORPORATION	CIVIL ACTION NO. 01-CV-2981
SMITHKLINE BEECHAM CORPORATION and BEECHAM GROUP, P.L.C. v. ENDO PHARMACEUTICALS, INC.	CIVIL ACTION NO. 01-CV-5770

AFFIDAVIT OF DR. CHRISTOPHER T. RHODES IN SUPPORT OF SMITHKLINE BEECHAM CORPORATION AND SMITHKLINE BEECHAM, P.L.C.'S OPPOSITION TO TORPHARM'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY OF CLAIMS 1 AND 2 OF U.S. PATENT NO. 6,113,944

Affidavit of Dr. Christopher T. Rhodes

I, Dr. Christopher T. Rhodes, state as follows:

1. I have been retained by Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P. to testify on behalf of SmithKline Beecham Corporation and SmithKline Beecham, p.l.c. (collectively referred to as "SB"), as an expert in the field of solid dosage formulations.

I. QUALIFICATIONS

2. My curriculum vitae (a copy of which is attached as Exhibit A) shows my background, experience, and qualifications. I am Professor of Applied Pharmaceutical Sciences at the University of Rhode Island. I am also President of PharmaCon of Rhode Island, a company which provides consulting services on pharmaceutical products to government agencies, pharmaceutical companies, and other entities in the United States, Canada, the United Kingdom, and other European Union countries.

3. I obtained my B. Pharm. (Honors) and Ph.D. degrees from the University of London in 1961 and 1964, respectively. From 1964 to 1965, I was a SmithKline French Research Fellow in Industrial Pharmacy at Purdue University. Since 1965, I have held academic posts at Portsmouth University, the University of British Columbia, State University of New York at Buffalo, and since 1975, at the University of Rhode Island.

4. Working with a group of graduate students, technicians, and post-doctoral fellows, I have conducted extensive research on the formulation, production, evaluation, and regulatory approval of drug products. In particular, I have examined the formulation of tablets, the compaction process whereby tablets are manufactured, stability of drug products (including stability in channels of distribution), and pharmaceutical process validation. Also, I have focused considerable attention on the mode of action of tablet disintegrates, the dissolution process, and other factors affecting the bioavailability of drugs. I have authored over two

hundred papers and I am an editor of five books, one of which, *Modern Pharmaceutics*, now in its fourth edition, has been widely accepted as a standard teaching and reference text.

5. My services as a consultant have been used by many pharmaceutical companies. I also have worked for the Internal Revenue Service, the U.S. Army Chemical Warfare Defense Command, the World Bank, and the FDA. Additionally, I served on two FDA Expert Advisory Committees (Generic Drugs and Compounded Drugs), and the United States Pharmacopoeia ("USP") Committee of Revision (Dissolution and Bioavailability and Stability subcommittees).

6. I have been admitted as an expert witness on drug products by courts and other bodies in the United States, Canada, Australia, Korea, Israel, and the Netherlands.

II. The Claims and Disclosure of the '944 Patent

7. Claim 1 of the '944 patent reads as follows:

> 1. A pharmaceutical composition in tablet form containing paroxetine, produced on a commercial scale by a process which comprises the steps of:
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> a) dry admixing paroxetine and excipients in a mixer to form a mixture; or
>
> b) dry admixing paroxetine and excipients, compressing the resulting combination into a slug material or roller compacting the resulting combination into a strand material, and milling the prepared material into a free flowing mixture, and
>
> c) compressing the mixture into tablets.

8. Claim 2 of the '944 patent reads as follows:

> 2. A pharmaceutical composition in tablet form according to claim 1 containing an amount of paroxetine selected from 10 mg, 20 mg, 30 mg, 40 mg and 50 mg, wherein the amount of paroxetine is expressed as the free base, produced on a commercial scale by a process which comprises the steps of:
>
> a) dry admixing paroxetine and excipients in a mixer to form a mixture; or

b) dry admixing paroxetine and excipients, compressing the resulting combination into a slug material or roller compacting the resulting combination into a strand material, and milling the prepared material into a free flowing mixture, and

c) compressing the mixture into tablets using a single punch or rotary tablet machine.

9. One of skill in the art[1] would understand that the claims of the '944 patent are directed to tablets, intended to be taken by patients as a therapeutic agent, containing any pharmaceutically acceptable salt form or other forms of paroxetine. They would also understand that the tablets are made in an amount sufficient to sell them in commerce. (*See* DX 1, '944 patent, col. 2, lines 45-67.)[2]

10. The person of skill in the art would also understand from the claims and specification of the '944 patent that the tablets are made by dry admixing and compressing processes. The '944 patent's specification does not suggest that such a dry admixing process had been previously used to make paroxetine tablets on a commercial scale.

11. The disclosure of the '944 patent states that "[i]t has been surprisingly found that formulation of paroxetine into tablets can be carried out reliably and on a commercial scale using a formulation process in which water is absent, such as by direct compression or by dry granulation." (DX 1, '944 patent, at col. 1, lines 38-42.) This would lead one of skill in the art to the conclusion that, prior to the invention of the '944 patent, wet granulation was the desired process for making paroxetine tablets on a commercial scale. This conclusion is supported by

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[1] In my opinion, a person of ordinary skill in the art of pharmaceutical technology, and particularly oral solid dosage forms, would have a B.S. in either pharmacy (or some related discipline such as chemistry, or chemical engineering), and at least two years experience in pharmaceutical formulation of solid dosage forms.

[2] When possible, I have cited to the exhibits relied on and attached to TorPharm's Memorandum of Law. I have cited these exhibits as DX __.

the statement in the '944 patent that "[t]o date, all tablets which have been sold have been formulated using an aqueous granulation process." (DX 1, '944 patent, at col. 1, lines 37-38.)

12. The '944 patent also explains that tablets made by wet granulation often developed an undesirable pink hue. However, if the paroxetine tablets were made by dry admixing and compressing, the pink hue was much less likely to develop. As I understand it, the development of the pink hue in the wet granulation process was intermittent, where some batches of tablets turned pink while other batches remained white.

13. One of skill in the art would recognize an intermittent stability problem, in the context of tablet formulation, as one of the most difficult problems to solve. Because the problem arises only some of the time, despite using the same active drug substance, excipients, process, and machinery, it is difficult to determine the exact cause of the problem.

14. Pharmaceutical manufacturers must avoid intermittent changes during the tableting process as they indicate a process that is "out of control." An out of control process is a concern from a regulatory perspective because it likely will continue to sporadically produce future batches of finished product that fail quality control testing. As a result, the FDA may force the company to withdraw the product from the market until the problem is resolved. If the problem were thought to be serious enough, the FDA could issue a recall of the product.

15. A person of skill in the art faced with an intermittent discoloration problem would need to investigate the problem in order to determine the appropriate solution. For such an investigation, a drug formulator would recognize that any number of factors could be the cause of the intermittent pink hue problem. There are several possible factors that one skilled in the art would consider in addressing this problem, including:

- The intermittent pink hue could very like result from an oxidation-type reaction in the composition.

- The apparent pH of the excipients or the apparent solid state pH of the microenvironment of the tablet could be a factor affecting the problem.

- The pink hue could result from a heat transfer problem during compaction.

- The pink hue could be caused by one or more of the tablet excipients (or minor impurity in one of the excipients) interacting with the active ingredient.

- It may be caused by an interaction in the wet state of some of the components in the formulation.

- The problem could occur during production from a reaction catalyzed by light.

16. In my opinion, however, one skilled in the art most likely would consider that the appearance of an intermittent pink hue meant that an oxidation reaction was occurring. These types of reactions, while relatively rare, are serious matters and very difficult to "formulate around." (*See* Ex. B, *Drug Stability Principles and Practice*, p. 113 (J.T. Carstensen and C.T Rhodes eds., 3rd Ed., 2000).) Thus, those skilled in the art most likely would have first attempted to ameliorate the problem by adding an anti-oxidant or chelating agent to the tablet formulation or to remove oxygen and/or use a nitrogen blanket during the tableting process.

17. Moreover, one of ordinary skill in the art would not first consider moisture to be the cause of the intermittent pink hue. As stated in the '944 patent, all of the tablets were made by wet granulation. (DX 1, '944 patent, at col. 1, lines 35-38.) Thus, if water were the problem, every batch of paroxetine tablets made by wet granulation would have turned pink. Therefore, reduction of water in the manufacturing process would be one of the last factors I, as well as others skilled in the art, would have considered. I find it surprising and unexpected that the intermittent pink discoloration was significantly decreased by changing the tableting formulation from wet granulation to dry admixing and compressing. In particular, it is surprising that total

exclusion of all water is apparently not necessary to achieve this result. The patent only requires avoiding "the wholesale addition of water." (DX 1, '944 patent, col. 1, lines 59-62.)

III. Tableting

A. Tableting processes

18. In essence, the process of tablet manufacture consists of allowing a mixture of drug and excipients[3] to flow into a hollow metal tube (the die) at the bottom of which is a piston (the lower punch). Once a sufficient amount of the drug mixture has entered the die another piston (the upper punch), enters the top of the tube and force is exerted on to the powder bed by the punches so that, if the components of the formulation have appropriate physical and chemical properties, a compressed tablet is produced.

19. However, many powder mixes of drug and excipients do not have appropriate properties to allow tablets to be made on a tablet press. Thus, a granulation step is normally required before compaction is effected. Wet granulation is the traditional granulation process and the conventional method of manufacturing compressed tablets. As of December 15, 1993, wet granulation was the conventional method of admixture for the commercial scale production of paroxetine tablets.

20. Wet granulation involves mixing the components of the drug formulation (active drug substance and excipients[4]) with a carefully controlled amount of an aqueous or non-aqueous granulating fluid (water is the commonly used granulating fluid), so that the particles stick

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[3] The term excipient is used for materials, other than the drug, which are included in a dosage form in order to facilitate manufacture, improve stability, or function in some other way to improve the properties of the dosage form. For example, pharmaceutical compressed tablets normally include a disintegrant, such as sodium starch glycolate, which promotes the break-up of the tablet once it has been ingested by a patient. Tablet lubricants, such as magnesium stearate, reduce the frictional forces between the powder bed/tablet and the die wall.

[4] It is common practice to add only part of the tablet disintegrant, about 50% of the total, at this stage of the process (this is the intragranular disintegrant.)

together to form agglomerates. The addition of the granulating fluid was traditionally performed under the direct supervision of an experienced and highly paid technician who could judge exactly when the appropriate amount of granulating fluid had been added. After the granules have been formed by agglomeration, they are dried and screened to the appropriate size. (*See* Ex. C, J.T. Carstensen, *Pharmaceutics of Solids and Solid Dosage Forms*, at 147-149 (1977).) The various components of the wet granulation formulation are intimately mixed together so that the homogeneity (thoroughness of mix) is generally excellent and as a result, the granules have good flow and compaction properties and are normally approximately spherical in shape. Prior to compaction but after the granules have been formed, a tablet lubricant, such as magnesium stearate, as well as the remaining disintegrant, such as sodium starch glycolate, are added (extra-granular).

21. Granules can also be formed without the addition of a granulating fluid. Dry granulation tableting, also known as slugging or roller compacting, usually involves mixing or blending the components required in the tablet (i.e., any excipients and the active ingredient) without the wholesale addition of water or another granulating fluid, and compressing the mixture into a slug or roller compacting it into strand material. The slug or strand material is then milled (broken apart) to form free-flowing granules. These granules are then compressed into tablet form. (*See* Ex. C, at 161.)

22. The granulation process, and especially wet granulation, produces tablets of excellent quality but traditionally required several pieces of equipment and was labor-intensive, thereby making it costly. Thus, during the 1960's and 1970's many pharmaceutical scientists, including myself, expended considerable time and energy in exploring methods of producing tablets that do not involve a granulation process. In particular, we evaluated excipients such as

certain forms of microcrystalline cellulose (Avicel PH 102), and granular dicalcium phosphate, as matrices for tablets. The flow and compaction properties of these materials (generally of larger particle size), are such that drugs and other excipients can be mixed with them so that the resultant mixture could be "directly compressed" into tablets. Thus, there is no need for a granulation step.

23. The method of tablet production described above is generically termed "direct compression." Like granulation, this method is be subdivided into two categories, dry direct compression and wet direct compression.

24. In dry direct compression there is no wholesale addition of water or granulating fluid at any processing step in the total tablet manufacturing process. The process involves dry mixing or dry blending all materials required in the tablet (i.e., any excipients and active ingredient) and compressing the mixture directly into tablet form. (*See* Ex. D, R.F. Shangraw, "Compressed Tablets by Direct Compression," *Pharmaceutical Dosage Forms*, p. 196 (H.A. Liberman, L. Lachman, J.B. Schwartz, eds., 2nd Ed. 1989).)

25. Wet direct compression involves mixing or blending all materials required in the tablet (i.e., any excipients and active ingredient) and then directly compressing the mixture into tablet form. The active ingredient in a wet direct compression process is dissolved in a solvent, sprayed onto an excipient, and then dried before the compaction process. Despite having a wet processing step, the wet direct compression process does not form granules or agglomerates and can, therefore, correctly be called direct compression. (*See* Ex. D, at 196.)

26. The most common concerns with respect to direct compression formulations are content uniformity, weight uniformity, and flow difficulties. (*See* Ex. E, Khan and C.T. Rhodes, *The Production of Tablets by Direct Compression*, Canadian Journal of Pharm. Sciences, Vol. 8,

No. 1, p. 3-4 (1973).) Because the active ingredient and excipients are not held together in granules (as they are in a wet granulation or dry granulation process), they often have a tendency to "unblend" or segregate after they have been blended together. This is particularly true when there is a "difference in particle size or density between drug and excipient particles." (DX 27, '535 patent, col. 2, lines 56-61.) If the resulting tablets do not contain a uniform mixture of active ingredient and excipient, the entire batch may fail specification and be rejected.

27. Additionally, there is no guarantee that a directly compressible formulation, sufficient to make smaller batches of tablets, will be robust enough for use during commercial scale production. In particular, powder flow of direct compression tablet blends, which may be acceptable at low tablet production rates used for laboratory and clinical trials, may be unacceptable for commercial scale production.

B. Different tableting processes result in different products

28. Pharmaceutical formulators know that a tablet bears the fingerprint of the process by which it was made. That is, although a batch of tablets made by wet granulation may be clinically equivalent to a batch of tablets made by dry direct compression, the tablets comprising those two separate batches will possess different and identifiable physical characteristics.

29. The most obvious physical difference between a paroxetine wet granulation formulation and a paroxetine dry admixing and compressing formulation is the development of a pink hue upon compressing the paroxetine wet granulation formulation into a tablet. (DX 1, '944 patent, at col. 1, lines 35-38.) Paroxetine tablets made using dry admixing and compressing are "less likely to develop a pink hue," and are therefore, in my opinion, superior products. (DX 1, '944 patent, at col. 1, lines 44-46.)

30. Because the components of a wet granulation formulation are intimately mixed together, the overall content uniformity of a wet granulation formulation will likely be better

than the content uniformity of a dry direct compression formulation. However, the wet granulation formulation will generally exhibit different content uniformity with respect to the lubricant and disintegrant because these are extra-granular components (added after the granules have formed). (¶ 20, *supra*.) Thus, there will be areas in a wet granulated tablet where no lubricant will be found, whereas in a dry direct compression formulation the lubricant will be dispersed more evenly throughout the tablet. Similarly, the concentration of the disintegrant will, at a microscopic level, show significant variations in wet granulated tablets because of the extra-granular nature of about 50% of this component. (*See* n. 4, *supra*.)

31. Moreover, the wet granulation process uses granules that can retain some of their spherical shape when compressed into a tablet. In contrast, the direct compression process does not use granules and thus, remnants of a spherical structure will not be found.

32. It is my opinion, therefore, that tablets made by different processes will have different physical properties and are thus different products. Furthermore, it is my opinion that paroxetine tablets made by dry admixing and compressing are different from and superior to tablets made by wet granulation, because the dry admixed and compressed paroxetine tablets are less likely to develop an undesirable pink hue.

IV. References Relied On By TorPharm

33. When drug formulators are asked to formulate an active drug substance into a solid dosage form they will be interested in the drug's tableting properties, such as particle size, crystalline structure, and compression characteristics. They will also be interested in knowing whether the active drug substance is sensitive to water or any other solvent, and whether the drug substance is known to chemically interact with a specific excipient. This type of information will enable the formulator to select an appropriate formulation that will result in a product that

can be reliably produced with minimum batch to batch variability, and thus have an optimal chance of gaining FDA approval.

34. It is my opinion, provided in detail below, that none of the references relied on by TorPharm disclose a paroxetine tablet made on a commercial scale by dry admixing and compressing. Nor do the references provide any reason or motivation to one of skill in the art to use a dry admixing and compressing process to make paroxetine tablets on a commercial scale or to reduce the intermittent occurrence of the pink hue associated with paroxetine tablets made on a commercial scale by wet granulation.

1. The '723 patent

35. It is my opinion that the '723 patent does not disclose or suggest making paroxetine tablets on a commercial scale by dry admixing and compressing. If anything, the patent directs one to make paroxetine tablets by wet granulation.

36. The disclosure of the '723 patent, which is not a drug formulation patent, is entirely too generic and does not disclose any of the physical characteristics of paroxetine. Thus, it does not teach anything relevant to the claims of the '944 patent. The patent itself is directed to "crystalline paroxetine hydrochloride hemihydrate as a novel material. . ." (DX 6, '723 patent, at col. 1, lines 57-59.) It does not mention any type of tableting process and certainly does not disclose paroxetine tablets made on a commercial scale by dry admixing and compressing.

37. While the '723 patent does mention paroxetine tablets (*see* DX 6, '723 patent, at col. 5, lines 60-61), it fails to provide a description of the tableting process.

38. I note that col. 5, lines 62-64 of the '723 patent states "[t]he composition of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing." (DX 6, '723 patent, at col. 5, lines 62-64.)(Emphasis added.) The term "blending" can relate to liquid dosage forms and solid dosage forms. The term "filling"

generally relates to capsules. The term "compression" generally relates to tablets, although "compression" can also be used in a formulation process for some types of capsules as well. However, the most "conventional" tableting process in 1993 was wet granulation. (*See* ¶ 19.) Hence, if one of skill in the art were to actually make paroxetine tablets based on the disclosure of the '723 patent, those tablets would be wet granulated.

39. Accordingly, the '723 patent does not disclose or suggest making paroxetine tablets on a commercial scale by a dry admixing process. Further, if a drug formulator were to make tablets based on the disclosure in the '723 patent, those tablets would be wet granulated. Thus, the paroxetine tablets of the '723 patent would be different from those claimed in the '944 patent.

2. The '281 patent application

40. The '281 patent application does teach paroxetine tablets. Importantly, however, the only example in the application providing a tablet formulation would lead one of skill in the art to make paroxetine tablets by wet granulation.

41. The '281 patent application is directed to the use of paroxetine for the treatment of senile dementia. (*See* DX 17, '281 patent application, Abstract.) Like the '723 patent, pages two and three of the '281 patent application describe nearly all possible dosage forms and types of excipients. (*Id.* at pp. 2-3.) However, the '281 patent application does not provide the particle size, crystalline structure, or compressibility characteristics of paroxetine to determine which dosage form to use.

42. The '281 patent application includes a tablet formulation in Example 1. (*Id.* at p. 5.) The components of the Example 1 tablet formulation are those of SB's wet granulation commercial product as set forth in SB's New Drug Application.

43. Example 1 of the '281 patent application states "[t]he following were mixed together in a conventional manner and compressed into a tablet in a conventional manner." (*Id.* at p. 5, lines 20-21 emphasis added.) As of 1993, wet granulation was the conventional tableting process. (*See* ¶ 19.) Thus, when persons of skill in the art see the term "conventional," they would most likely think of a wet granulation process.

44. The formulation of Example 1 includes "Hydroxypropylmethyl cellulose 2910," also known as HPMC. HPMC is a well known wet binder and among cellulose derivatives, it is the most common. (*See* Ex. F, *Modern Pharmaceutics*, p. 372 (Gilbert S. Banker & Christopher T. Rhodes eds., 2nd Ed. 1989).) If HPMC is to be used as a wet binder, it should make up from about 5-10% weight/weight of the total tablet formulation. (*Id.*) The weight of the tablet of Example 1 is 300.00 mg and includes 15.00 mg of HPMC, which is 5% of the total tablet weight. (DX 17, '281 patent application at p. 5, lines 20-29.) Thus, one of skill in the art would infer from the inclusion of HPMC, at 5% of the total tablet weight, that it is being used as a wet binder in a wet granulation process and that the disclosed tablet is a wet admixed paroxetine tablet.

45. Because the only formulation example in the '281 patent application leads me to conclude that paroxetine tablets should be made by wet granulation, it is my opinion that the '281 patent application does not teach paroxetine tablets made on a commercial scale by dry admixing and compressing. Moreover, the '281 patent application does not motivate me or a person of ordinary skill in the art to make a paroxetine tablet by dry admixing and compressing in order to reduce the development of a pink hue.

46. I note that in an International Preliminary Examination Report an international patent examiner stated that Example 1 of the '281 patent application "describes paroxetine (hydrochloride hemi-hydrate) formulated into tablets, wherein water is absent[.]" (DX 13 at

p. 00027.) As I have explained above, Example 1 actually discloses a wet granulation paroxetine formulation. The patent examiner did not mention the phase "conventional manner," nor did he address HPMC. (DX 13 at p. 00027.) It is my opinion that the patent examiner did not focus on these particular elements and thus, incorrectly concluded that Example 1 discloses "paroxetine formulated into tablets, wherein water is absent."

3. **The '122 patent**

47. I have reviewed EP-A-0188081 ("EP '081"), which is listed on the cover of the '944 patent under "Foreign Patent Documents. (*See* DX 1, '944 patent, front cover; Ex. G.) The disclosure of EP '081 is essentially identical to the disclosure of the '122 patent, with both having similar Titles, identical Methods, and identical Tables providing results. (*Compare* DX 11, '122 patent with Ex. G, EP '081.) In fact, the statement in the '122 patent relied on by TorPharm is reproduced in EP '081:

> "paroxetine or a pharmaceutically acceptable salt thereof . . [is] administered in the form of a unit-dose pharmaceutical composition in which it is combined with a pharmaceutically acceptable carrier; such as a unit-dose oral or parenteral composition.
> Examples of oral compositions include tablets and capsules. . ."

(*See* TorPharm Mem. at p. 16, citing DX 11, '122 patent, col. 1, lines 38-44.)

> "paroxetine or a pharmaceutically acceptable salt thereof . . [is] administered in the form of a unit-dose pharmaceutical composition in which it is combined with a pharmaceutically acceptable carrier; such as a unit-dose oral or parenteral composition.
> Examples of oral compositions include tablets and capsules. . ."

(*See* Ex. G, EP '081, p. 2, lines 13-19.)

48. Thus, I conclude that EP '081 provides the exact same teaching as the '122 patent.

49. In my opinion, the '122 patent, which is not a drug formulation patent, teaches no more than the '723 patent and less than the '281 patent application discussed above.

50. The '122 patent is directed to a method of treating obesity by administering paroxetine. (*See* DX 11, '122 patent, at col. 1, lines 18-23.) The '122 patent does not provide any information with respect to the tableting properties of paroxetine nor does it identify any specific tableting process or tablet formulation. As such, the '122 patent does not provide one of skill in the art with any information relevant to developing a paroxetine tablet.

51. The passage quoted in paragraph 50 that TorPharm relied on states that paroxetine should be administered in a unit-dose form. This teaches nothing with respect to any dosage form, let alone tablets.

52. The '122 patent not only discloses tablets and capsules, it also discloses that the oral composition may be in the form of a liquid, a solution, an emulsion, syrup, elixir, or in the form of a dry product for reconstitution with water or any other pharmaceutically acceptable liquid vehicle. (*See* DX 11, '122 patent, col. 1, lines 46-50.) Almost every conceivable dosage form is disclosed in a generic sense.

53. Further, it is my opinion that the '122 patent teaches nothing more than the '723 patent and provides even less information than the '281 patent application. The '281 patent application, although disclosing a wet granulation tablet formulation, at least provides an example of a paroxetine formulation.

54. The '122 patent does not disclose a paroxetine tablet made on a commercial scale by dry admixing and compressing. Further, it is my opinion that the '122 patent does not suggest or motivate one skilled in the art to make paroxetine tablets on a commercial scale by dry admixing and compressing or to do so in order to reduce the development of the pink hue associated with paroxetine tablets made on a commercial scale by wet granulation.

4. The '669 patent

55. The '669 patent corresponds to EP-A-0269303 ("EP '303"), which is listed under "Foreign Patent Documents" on the front of the '944 patent. (*See* DX 1, '944 patent, front cover; Ex. 11.) I have reviewed EP '303 and determined that its disclosure is essentially identical to that of the '669 patent. In fact, the statement relied on by TorPharm is reproduced, *verbatim*, in EP '303. (*Compare* DX 21, '669 patent, at col. 1, lines 62-68 with Ex. H, EP '303, at p. 2, lines 33-38.)

56. TorPharm cites the following passage from the '669 patent:

> Paroxetine or a salt thereof may be formulated for administration by any route, and examples are oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may, if desired, be designed to give slow release of paroxetine.
>
> The medicaments may, for example, be in the form of tablets . . .

(*See* TorPharm Mem. at p. 17, citing DX 21, '669 patent, at col. 1, lines 62-68.) This passage teaches nearly every dosage form but fails to provide any specific formulation or tableting process. Thus, the '669 patent is not a drug formulation patent. The '669 patent also fails to provide any information with respect to the tableting properties of paroxetine. Accordingly, one of skill in the art would find no information relevant to the development of a paroxetine tablet formulation.

57. The '669 patent, much like the '723 patent discussed above, discloses that "solid medicaments may be obtained by conventional methods of blending, filling, tableting or the like." (DX 21, '669 patent, at col. 2, lines 14-15.) As I stated previously, the terms "blending" and "filling" refer to the process for making almost any dosage form and thus provide insufficient information for identifying a specific dosage form.

58. Furthermore, the '669 patent does not disclose anything more relevant than the '723 patent or the '122 patent and, because it does not even provide a tablet formulation, it teaches less than the '281 patent application.

59. In my opinion the '669 patent does not disclose a paroxetine tablet made on a commercial scale by dry admixing and compressing. Further, the '669 patent does not suggest or motivate one of skill in the art to prepare paroxetine tablets on a commercial scale by dry admixing and compressing or to do so in order to reduce the intermittent development of the pink hue.

5. Paxil sales

60. SB disclosed in the '944 patent that paroxetine "has been approved for human use and is being sold in many countries around the world as an anti-depressant agent." (DX 1, '944 patent, at col. 1, lines 31-33.) SB also disclosed that those paroxetine tablets were made by aqueous granulation. (DX 1, '944 patent, at col. 1, lines 37-38.)

61. As explained above, different tableting processes yield tablets with different physical properties. (*See* ¶¶ 28-32.) The '944 patent describes the most apparent difference between paroxetine tablets made by wet granulation and tablets made by dry admixing and compressing i.e., the increased formation of a pink hue with the use of a wet granulation process. (DX 1, '944 patent, at col. 1, lines 35-36 and 44-46.) The commercial scale paroxetine tablets made by dry admixing and compressing are superior to those previously make by wet granulation because they are less likely to turn pink.

62. Moreover, one of skill in the art would have been able to determine that SB used wet granulation and, therefore, have been motivated to make paroxetine tablets using a wet granulation process. The skilled artisan would conclude that SB had already determined wet granulation was the preferred tableting process.

63. Because SB's tablets, which were sold prior to December 14, 1993, were made by a wet granulation process, they are different from the tablets produced by the process claimed in the '944 patent and inferior, due to the development of the pink hue. As a result, the sale of Paxil® tablets made by wet granulation does not teach paroxetine tablets made on a commercial scale by dry admixing and compressing. Further, the sale of Paxil® tablets made by wet granulation would motivate a person of skill in the art to make paroxetine tablets on a commercial scale by wet granulation, thereby teaching away from the invention of the '944 patent, that is, paroxetine tablets made on a commercial scale by dry admixing and compressing.

6. The '810 patent

64. In my opinion, one of skill in the art would not consider the '810 patent to teach anything remotely relevant to the claims of the '944 patent because it is not directed to paroxetine nor does it disclose a paroxetine tablet. The '810 patent is directed to benzanilide derivatives and to a process for their preparation. (*See* DX 23, '810 patent, at col. 1, lines 1-3.) Paroxetine is not benzanilide nor one of its derivatives.

65. The only reference to paroxetine in the '810 patent is with respect to a combination therapy with benzanilide or one of its derivatives, stating that "the compounds according to the invention [benzanilide derivatives] may advantageously be used in **conjunction with** one or more other therapeutic agents. . ." (DX 23, '810 patent, at col. 6, lines 26-28.)(Emphasis added.) This would lead one of skill in the art to conclude that paroxetine, in any number of dosage forms, could be taken at the same time as the benzanilide derivative. The '810 patent does not disclose combining paroxetine and a benzanilide derivative into one solid dosage form, let alone a tablet made by dry admixing and compressing. In fact, the '810 patent states "[i]n using a compound of general formula (I) . . . and one or more

therapeutic agents it may be preferable to employ the active ingredients in the form of separate pharmaceutical formulations." (DX 23, col. 6, lines 63-67.) (Emphasis added.)

66. The '810 patent's disclosure of tablets is in reference to acceptable formulations for benzanilide derivatives, not paroxetine. (DX 23, '810 patent, at col. 7, lines 24-31.) Pharmaceutical Example 1 of the '810 patent discloses the production of a tablet containing "the compound of formula (I)," which is a benzanilide derivative. (DX 23, '810 patent, at col. 35, lines 18-41.) The '810 patent does not disclose or suggest producing a paroxetine tablet, let alone a paroxetine tablet made on a commercial scale by dry admixing and compressing. Accordingly, one of skill in the art would not consider the '810 patent to be remotely relevant to the claims of the '944 patent.

B. References cited by TorPharm do not motivate one of skill in the art to make paroxetine tablets by direct compression

67. In my opinion, TorPharm's references would not motivate one of skill in the art to make paroxetine tablets on a commercial scale by dry admixing and compressing.

1. The references are silent with respect to the intermittent pink hue

68. None of the references teach or suggest the use of dry admixing and compressing to address an intermittent discoloration problem. Specifically, all of the references fail to teach or even suggest the use of dry admixing and compressing to make paroxetine tablets on a commercial scale in order to reduce the intermittent occurrence of the pink hue associated with paroxetine tablet made by wet granulation.

69. As previously stated, SB initially marketed its paroxetine tablets made by a wet granulation process. The commercial scale batches of tablets, however, developed a pink hue on an intermittent basis despite using the same wet granulation process, the same equipment and the same granulating fluid (water). No one would assume water was the problem. If water were the

problem, then every batch of paroxetine tablets made by SB's wet granulation process would have turned pink.

70. Working from this premise, it would not have occurred to me, nor to one of skill in the art, to switch from a wet admixing process to a dry admixing process in order to resolve the pink hue. TorPharm's references do not contradict this. Further, it was not previously known that a dry tableting process could resolve an oxidation problem like the pink hue. Even today, experts in the area do not suggest dry admixing as potential remedies for oxidation degradation. (*See* Ex. I, K.C. Waterman, et al., "Stabilization of Pharmaceuticals to Oxidative Degradation," *Pharmaceutical Development and Technology*, 7(1), pp. 20-27 (2002).) Accordingly, it was surprising and unexpected that the use of dry admixing and compressing reduced the pink hue.

2. The prior art suggests making paroxetine tablets on a commercial scale by wet granulation

71. SB initially made its commercial scale batches of paroxetine tablets by wet granulation. This would have been apparent to persons who analyzed the Paxil® tablets and would have led them to conclude that wet granulation was the desired tableting process for the commercial scale production of paroxetine tablets. As a result, a drug formulator would actually be motivated to make paroxetine tablets on a commercial scale by wet granulation. Accordingly, in my opinion, the prior art does not suggest making paroxetine tablets on a commercial scale by dry admixing and compressing.

3. The economic desirability of direct compression neither guarantees feasibility nor motivates one of skill in the art

72. The four references describing the economic advantages of direct compression fail to disclose paroxetine or paroxetine tablets made on a commercial scale by dry admixing and compressing. (DXs. 14, 16, 24, and 27.) Further, they do not suggest the use of dry admixing

and compressing for paroxetine nor guarantee its feasibility. In fact, the references warn a drug formulator that direct compression is not always an available option. Finally, the references do not suggest using dry direct compression as opposed to wet direct compression.

73. The first textbook reference, TorPharm Exhibit 16, describes generally the process to follow when developing a tablet. (DX 16 at p. 64.) The reference, however, does not mention paroxetine. While the reference discloses that direct compression (without specifying wet or dry) is cheap and simple, it goes on to state that "it is this apparent simplicity which has caused so many initial failures . . ." (DX 16 at p. 148.) Thus, this reference warns the reader of the problems associated with using direct compression.

74. The second textbook reference, TorPharm Exhibit 24, simply provides descriptions of direct compression (without specifying wet or dry), dry granulation, and wet granulation, but does not suggest using any of these processes to make paroxetine tablets on a commercial scale. (DX 24 at pp. 318-322.) The reference goes on to state that "[t]here are a few crystalline substances, such as inorganic salts ( ), which may be compressed directly; but the vast majority of medicinal agents are rarely so easy to tablet." (DX 24 at p. 318, right col.) The reference also lists the limitations of direct compression. (DX 24 at p. 319.) Thus, in my opinion, the reference provides no assurance that paroxetine tablets can be made by dry admixing and compressing.

75. The '246 patent does not disclose dry admixing and compressing of paroxetine, but rather cyclophosphamide, a compound that inhibits tumor growth. (DX 14, '246 patent, Abstract.) Cyclophosphamide and paroxetine have entirely different chemical structures. The disclosure that cyclophosphamide can be dry admixed and compressed does not provide any reason for a drug formulator to believe that paroxetine can be dry admixed and compressed. To

the contrary, the '246 patent suggests that "only a very limited number of pharmaceutical substances" can be formulated like cyclophosphamide. (DX 14 at col. 1, lines 49-53.)

76. The final reference, the '535 patent, is directed to a carbonyl iron tablet made by direct compression. (*See* DX 27, '535 patent, at col. 1, lines 6-20.) It does not disclose paroxetine at all or suggest making paroxetine tablets on a commercial scale by dry admixing and compressing.

77. Further, although disclosing the economic benefits of direct compression, the '535 patent also discloses the limitations of direct compression, such as segregation, incompatibility of components and the limited number of directly compressible excipients. (*See* DX 27, '535 patent, at col. 1, line 40 to col. 2, line 15.)

78. Turning specifically to the economic advantages of direct compression, I have been promoting the virtues of direct compression for years and agree that, economically, every pharmaceutical manufacturer would want to use a direct compression formulation. Economics, however, do not dictate whether direct compression is feasible for a given active drug substance. If that were the case, then every single tablet would be made this way. Moreover, although disclosing the economic desirability of the direct compression process, these references do not suggest that paroxetine can or should be dry admixed and compressed.

79. The quality of a solid dosage form, in this instance tablets, is a pharmaceutical manufacturer's first priority. A tablet cannot be sold if it does not meet quality standards and, therefore, a company will ensure that its product is of the highest quality even if this means using a slightly more expensive tableting process. For example, it is well documented that drugs containing amino functional groups show signs of brown or yellow speckling if made into a

tablet by direct-compression using the common direct compression excipient spray-dried lactose. (*See* Ex. B at p. 6 .)

80. Further, there is relatively little advantage to shaving a few pennies from tablet production costs when an active drug substance is itself expensive to make. With respect to prescription drugs such as paroxetine, regulatory approval is required. Thus, a company will be most reluctant to use a possibly more economical tableting process if it cannot be sure it will result in a reproducible product. Moreover, the economic desirability of direct compression is not a guarantee that a specific active ingredient can be made into a tablet by a dry admixing before direct compression.

81. The economy of a process is less of a motivating factor, if a factor at all, to a drug formulator especially for prescription only drug products like paroxetine. It simply does not matter how cheap a process is if it doesn't work. Rather, a drug formulator would be more interested in the tableting properties of a given active drug substance. None of the references discuss any of these properties for paroxetine. Instead, they generically discuss the economic advantages of using direct compression as opposed to granulation. These references, however, do not suggest any advantages of dry admixing as opposed to wet admixing before direct compression.

4. Pharmacological class designation is irrelevant to the compressibility of a compound

82. U.S. Patents 5,071,854 ("the '854 patent") and 5,229,407 ("the '407 patent") disclose that specific 5-HT inhibitors, which are in the same pharmacological class (they act on the brain in a similar manner) as paroxetine, can be tableted using direct compression or granulation. (*See* TorPharm Mem. at p. 25; DX 25, '854 patent, at col. 10, lines 53-54; DX 26, '407 patent, at col. 6, lines 9-10.) In my opinion, the '854 and '407 patents, which do not discuss

paroxetine at all, do not provide any motivation to one of skill in the art to make a paroxetine tablet on a commercial scale by dry admixing and compressing.

83. The '854 and '407 patents each disclose that anti-depressant compounds within the same pharmacological class as paroxetine, but not paroxetine itself, can be made into tablets using direct compression or granulation. (DX 25, '854 patent, at col. 10, lines 53-54; DX 26, '407 patent, at col. 6, lines 9-10.) Pharmacological classification, however, is completely irrelevant with respect to the compressibility of a given compound. Simply because two compounds act on the brain in a somewhat similar fashion does not guarantee that they can both be made into tablets using the same process, because despite their similarities as pharmacological agents, they can have entirely different chemical structures, which dictate different tableting properties. Thus, a tableting method that works for one compound may very well not work for another. Information concerning pharmacological classification would therefore never be relied on by one of skill in the art in assessing the best tableting method to use for a particular compound.

84. Hence, the disclosure that certain anti-depressant compounds, not including paroxetine, can be directly compressed would not motivate one of skill in the art to dry admix and compress paroxetine into tablets on a commercial scale. Further, the '854 and '407 patents do not guarantee that paroxetine can be made into tablets using such a process. Nor do the '854 and '407 patents establish that dry admixing and compressing is an obvious choice for the commercial scale production of paroxetine tablets.

85. In summary, the references cited by TorPharm do not teach anything remotely relevant to formulating a paroxetine tablet. Further, none of the reference teaches paroxetine tablets made on a commercial scale by dry admixing and compressing. Moreover, none of the

references discussed above provide the motivation to one of skill in the art to make paroxetine tablets on a commercial scale by dry admixing or compressing or suggest using dry admixing and compressing to reduce the intermittent development of a pink hue. If anything, the references cited above would motivate one of skill in the art to make paroxetine tablets by wet granulation. (*See* DX 17, '281 patent application, at p. 5, Example 1; SB's Paxil® sales.)

Dated: 5 April 2002

C T Rhodes
Dr. Christopher T. Rhodes

Subscribed and sworn to me this 5th day of April, 2002

Sylvia Stran
Notary Public
Com Exp 6/7/02